Intraoperative oliguria predicts acute kidney injury after major abdominal surgery

AUTHOR(S):

T, Mizota; Y, Yamamoto; M, Hamada; S, Matsukawa; S, Shimizu; S, Kai

CITATION:

T, Mizota ...[et al]. Intraoperative oliguria predicts acute kidney injury after major abdominal surgery. British journal of anaesthesia 2017, 119(6): 1127-1134

ISSUE DATE:

2017-12

URL:

http://hdl.handle.net/2433/236676

Intraoperative oliguria predicts acute kidney injury after major abdominal surgery

T. Mizota[1,*], Y. Yamamoto[2], M. Hamada[1], S. Matsukawa[1], S. Shimizu[1], S. Kai[1]

[1]Department of Anaesthesia, Kyoto University Hospital, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

[2]Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoemachi, Sakyo-ku, Kyoto 606-8501, Japan

* Corresponding author: Toshiyuki Mizota

E-mail: mizota@kuhp.kyoto-u.ac.jp

Running title: Intraoperative Oliguria and Acute Kidney Injury

Abstract

Background: The threshold of intraoperative urine output under which the risk of acute kidney injury (AKI) increases is unclear. The aim of this large-scale retrospective cohort study was to investigate the relationship between intraoperative urine output during major abdominal surgery and the development of postoperative AKI, as well as to identify an optimal threshold for predicting the differential risk of AKI.

Methods: The authors retrospectively collected perioperative data for 3,560 patients undergoing major abdominal surgery (liver, colorectal, gastric, pancreatic or oesophageal resection) at Kyoto University Hospital. We evaluated the relationship between intraoperative urine output and the development of postoperative AKI as defined by recent guidelines. Logistic regression analysis was performed to adjust for patient and operative variables, and the minimum P-value approach was used to determine the threshold of intraoperative urine output that independently altered the risk of AKI.

Results: The overall incidence of AKI in the study population was 6.3%. Using the minimum P-value approach, a threshold of 0.3 mL kg^{-1} h^{-1} was identified, under which

there was an increased risk of AKI (adjusted odds ratio: 2.65; 95% confidence interval: 1.77–3.97; P < 0.001). The addition of oliguria under 0.3 mL kg^{-1} h^{-1} to a model with conventional risk factors significantly improved risk stratification for AKI (net reclassification improvement: 0.159; 95% confidence interval: 0.049–0.270; P = 0.005).

Conclusions: Among patients undergoing major abdominal surgery, intraoperative oliguria under 0.3 mL kg^{-1} h^{-1} was significantly associated with increased risk of postoperative AKI.

Keywords: Acute Kidney Injury; General Surgery; Monitoring, Intraoperative; Oliguria

Oliguria is widely viewed as an early marker of decreased kidney perfusion and impending acute kidney injury (AKI). The use of urine output (UO) to guide fluid therapy is often recommended by textbooks and guidelines[1–3] and is the standard practice in perioperative or critical care settings.[4 5]

Although oliguria is usually defined as UO less than 0.5 mL kg^{-1} h^{-1} in medical and surgical practice,[1 2] this threshold of UO is not supported by clinical evidence. The most recent update of the Surviving Sepsis Campaign guidelines does not mention the target value of UO;[3] this is in contrast to the previous version which recommended that the goals of initial resuscitation should include UO of ≥0.5 mL kg^{-1} h^{-1}.[6] Although serum creatinine (SCr) roughly represents the glomerular filtration rate,[7] UO is influenced by many factors including haemodynamics, sympathetic tone and aldosterone and anti-diuretic hormone levels. Therefore, thresholds of clinically significant oliguria, indicating renal hypoperfusion or impending AKI, may vary depending on clinical settings or patient conditions.

Fluid replacement targeting a higher UO tends to lead to increased fluid loading, which may be harmful; recent randomised trials have demonstrated that perioperative fluid

overloading markedly increases postoperative morbidity and length of hospital stay.[8–11] Conversely, allowing a lower UO may cause renal hypoperfusion and associated kidney damage. Therefore, identifying the optimal threshold for clinically significant oliguria may help optimise fluid management. However, to our knowledge, no study has attempted to identify an optimal threshold of intraoperative UO in surgical patients associated with increased risk of postoperative AKI.

The authors hypothesised that there is a threshold of intraoperative UO under which the risk of postoperative AKI increases. The aims of this large-scale retrospective study were 1) to investigate the relationship between intraoperative UO during major abdominal surgery and the development of postoperative AKI and 2) to identify an optimal threshold that predicts the differential risk of AKI.

Methods

Study design, Setting and Population

This single-centre retrospective cohort study was conducted in Kyoto University Hospital, which is a teaching hospital with 1,121 beds in Japan. The institutional review board approved the study protocol (approval number: R0672, 26 July, 2016) and waived the requirement for informed consent.

We included patients aged 18 years or older who underwent major abdominal surgery under general anaesthesia at Kyoto University Hospital from March 2008 to April 2015, i.e., from the institution of electronic database of surgical patients at our centre to the conception of this study. Major abdominal surgery included liver, colorectal, gastric, pancreatic or oesophageal resection by either laparotomy or laparoscopic approach. For patients who had more than one surgery that met the inclusion criteria during the study period, only the index case was included. Exclusion criteria were concurrent cardiac or urological procedures and patients with end-stage renal disease (i.e., estimated glomerular filtration rate of <15 mL min^{-1} 1.73 m^{-2}, as determined using a formula

validated in Japan,[12] or receipt of haemodialysis). In addition, patients who received diuretics (furosemide, human atrial natriuretic peptide or mannitol) intraoperatively were also excluded to eliminate the confounding of intraoperative use of diuretics.

Data collection

Data on study participants were collected from the electronic database and the electronic medical record system. To prevent variability in data collection, we collected data according to uniform criteria, especially regarding definitions of the medical conditions. Definitions of variables are listed in Supplementary Table S1. Procedure names recorded in the electronic database were used to identify and group major abdominal surgeries. The type of surgery was categorised into six groups (liver, colorectal, gastric, pancreatic, oesophageal and complex) and also divided into laparoscopic/non-laparoscopic surgery. 'Complex' means concomitant resection of two or more organs listed above. For each case, we calculated average intraoperative UO per hour based on body weight by dividing total intraoperative UO by duration of operating room stay and by the measured body weight.

Outcome

The primary outcome was AKI as determined by change in SCr according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition[13] (increase in SCr of ≥26.5 μmol L^{-1} within 48 h or ≥1.5 times baseline within 7 days after surgery). The most recent SCr measured before the surgery was used as the baseline value.

Statistical analyses

The analyses on the relationship between intraoperative UO and AKI were planned prior to data evaluation. We examined the unadjusted relationship between intraoperative UO and the risk of AKI using cubic spline function to identify any inflection point that could be used to dichotomise intraoperative UO into categories in a clinically meaningful way. If we observed an area of inflation, the optimal threshold for intraoperative UO was determined using the minimum P-value approach. This approach evaluated every possible threshold of intraoperative UO at intervals of 0.1 mL kg^{-1} h^{-1} in the multivariable logistic regression model and the intraoperative UO that demonstrated

the smallest statistically significant P-value was selected as the optimal threshold to dichotomise intraoperative UO. In the multivariable model, AKI risk index[14] was used to adjust for preoperative risk of AKI. This is a previously developed and validated risk index for predicting postoperative AKI in patients undergoing general surgery and includes age, gender, emergency surgery, intra-peritoneal surgery, diabetes mellitus, active congestive heart failure, ascites, hypertension and preoperative renal insufficiency. In addition, type of surgery, intraoperative blood loss (per kg body weight) and intraoperative continuous infusion of vasopressors were included in the model to adjust for type and invasiveness of surgery. The linearity of the association between intraoperative blood loss and the log-odds of AKI was assessed using cubic spline function and categorised if significant non-linearity ($P < 0.05$) was found. Multicollinearity among variables was assessed by the variance inflation factor with a reference value of 10. Discrimination and calibration of the multivariable model was assessed based on the c-index and the Hosmer–Lemeshow goodness-of-fit test, respectively. We assessed whether the addition of intraoperative UO to the model that only included AKI risk index and operative variables can improve the predictive ability

for AKI by calculating the category-free net reclassification improvement (NRI) and the integrated discrimination improvement (IDI).

We expected that the relationship between intraoperative UO and AKI would vary depending on patient or operative characteristics. Accordingly, we assessed this potential heterogeneity by subgroup analyses. We used the same model in the following subgroups: (1) AKI risk index (class 1/class 2/class 3–5); (2) type of surgery (liver/colorectal/gastric/others); (3) blood loss (<10 mL kg^{-1}/≥10 mL kg^{-1}) and (4) laparoscopic surgery (yes/no). We calculated the adjusted odds ratio for AKI in each subgroup and then, tested the interaction between subgroups and intraoperative UO.

We assessed the robustness of our findings using sensitivity analyses. Sensitivity models were constructed as logistic regression identical to the primary model above, except (1) with the primary outcome AKI redefined on the basis of SCr concentrations only up to 2 days postoperatively; (2) using severe AKI (stage 2–3 AKI according to KDIGO guidelines) as the outcome; (3) adjusting for the duration of the surgery; (4) using ideal body weight (determined with the body mass index method[15 16]) to calculate UO per body weight; (5) excluding patients who received intraoperative vasopressor

infusion; (6) excluding patients who received diuretics preoperatively and (7) excluding emergency surgeries.

The sample size was determined by including all eligible cases in the electronic database to maximise the power. Previous studies have suggested that at least 8–10 events per variable are required for reliable multivariable logistic regression analysis.[17] [18] We assumed approximately 500 eligible surgeries per year and predicted the prevalence of AKI to be 6% on the basis of published reports.[19–21] So we estimated that we can conduct multivariable logistic regression with approximately 24 variables using our dataset. As for missing values, we planned to conduct a complete case analysis if the missing values were below 5% because such an analysis might have been feasible in that case.[22]

All statistical tests were two tailed and a P-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the statistical program R (http://cran.r-project.org).

Results

Fig. 1 shows the flow diagram of this study. A total of 3,804 index major abdominal surgeries were identified in the electronic database spanning an approximately 7-year period from March 2008 to April 2015. After excluding patients with end-stage renal disease (n = 39) and those who received diuretics during the surgery (n = 201), 3,564 patients met the inclusion criteria of this study. Among these patients, data on intraoperative UO were missing in three patients and data on intraoperative blood loss were missing in one patient. Overall, cases with any missing predictor were 4 in number (0.1%); therefore, we conducted complete case analysis leaving 3,560 patients for further evaluation.

Study participants were aged 19–94 years, and 38.7% were women. The most common surgeries were liver resection (31.9%) and colorectal resection (29.6%). The median intraoperative UO for the study population was 0.81 mL kg^{-1} h^{-1}.

Of the 3,560 patients included in this study, 226 patients (6.3%; 95% CI: 5.6%–7.2%) developed AKI; patients with AKI had a significant increase in in-hospital mortality (6.6% vs. 0.8%, $P < 0.001$) and prolonged hospital stay (median: 26 vs. 15 days, $P <$

0.001). Table 1 shows patient characteristics and operative variables stratified by the AKI status. Patients who developed AKI had higher AKI risk index, had more blood loss and were more likely to receive intraoperative vasopressor infusion. Intraoperative UO in patients with AKI was lower than in those without. The cubic spline relating intraoperative UO to AKI was negatively sloped with inflection point at approximately 0.3–0.4 mL kg^{-1} h^{-1} after which the probability of AKI almost plateaued (Fig. 2). Based on this result, the range from 0.1 to 1.0 mL kg^{-1} h^{-1} was selected for determining the optimal threshold for intraoperative UO and possible thresholds at intervals of 0.1 mL kg^{-1} h^{-1} were considered. Using the minimum P-value approach, multivariable analysis demonstrated that the ideal threshold of intraoperative UO was 0.3 mL kg^{-1} h^{-1} (Supplementary Table S2). An intraoperative UO of <0.3 mL kg^{-1} h^{-1} occurred in 11.3% of patients. These patients had a higher AKI risk index, were more likely to undergo laparoscopic surgery and had less blood loss and lower net fluid balance (Supplementary Table S3). The incidences of AKI were 10.2% and 5.9% in patients with intraoperative UO of <0.3 and ≥0.3 mL kg^{-1} h^{-1}, respectively.

Multivariable analysis demonstrated that intraoperative UO of <0.3 mL kg^{-1} h^{-1} was

independently associated with the development of AKI (adjusted odds ratio: 2.65; 95% CI: 1.77–3.97; P < 0.001; Table 2). In this multivariable analysis, intraoperative blood loss was categorised into three groups (<10 mL kg^{-1}, 10–<20 mL kg^{-1} and ≥20 mL kg^{-1}) based on the result of cubic spline function analysis (Supplementary Fig. S1). Each variable included in the models demonstrated a variance inflation factor of <10, suggesting no multicollinearity. Both multivariable models without/with intraoperative UO demonstrated good discrimination [c-indices: 0.782 (95% CI: 0.751–0.813) and 0.791 (95% CI: 0.760–0.821), respectively] and calibration (P-values for Hosmer–Lemeshow goodness-of-fit test: 0.414 and 0.164, respectively).

We found that the category-free NRI for the addition of intraoperative UO to the model that only included AKI risk index and operative variables was 0.159 (95% CI: 0.049–0.270; P=0.005; Table 3). The IDI for the addition of intraoperative UO was 0.009 (95% CI: 0.003–0.015; P=0.003).

Because oliguria is usually defined as diuresis of less than 0.5 mL kg^{-1} h^{-1}, we carried out additional analysis calculating the risk of AKI associated with milder oliguria (intraoperative UO of 0.3–<0.5 mL kg^{-1} h^{-1}) while excluding patients with

intraoperative UO of <0.3 mL kg^{-1} h^{-1}. There was not a statistically significant risk of AKI for intraoperative UO of 0.3–<0.5 mL kg^{-1} h^{-1} (adjusted odds ratio: 1.37; 95% CI: 0.88–2.13; P = 0.160).

Subgroup analyses based on the AKI risk index, type of surgery, blood loss and laparoscopic surgery yielded wider confidence intervals but did not substantially affect the point estimates for the impact of intraoperative UO of <0.3 mL kg^{-1} h^{-1} on AKI, suggesting that there was no interaction between these variables and intraoperative UO (Fig. 3). The relationship between intraoperative UO and AKI was qualitatively preserved across sensitivity analyses (Supplementary Table S4).

Discussion

In this cohort study of 3,560 patients undergoing major abdominal surgery, we found that intraoperative UO of <0.3 mL kg^{-1} h^{-1} was independently associated with postoperative AKI. 11.3% of patients had an intraoperative UO of <0.3 mL kg^{-1} h^{-1}, and the risk for AKI increased by approximately 2.7 times in these patients. NRI analysis demonstrated that intraoperative UO of <0.3 mL kg^{-1} h^{-1} significantly improved risk stratification for AKI compared with assessment limited to AKI risk index and operative variables. In contrast, intraoperative UO of 0.3–<0.5 mL kg^{-1} h^{-1} was not significantly associated with increased risk of AKI.

Previous studies in perioperative settings failed to demonstrate significant association between intraoperative UO and AKI,[23 24] and recent review suggested that intraoperative UO is not related to perioperative renal function.[25] Alpert *et al.*[23] reported that there was no significant correlation between intraoperative UO and postoperative renal function in patients undergoing abdominal aortic reconstruction. However, this study included only 137 patients and therefore, was too underpowered to conclude the predictive value of intraoperative UO for postoperative AKI. Moreover, it included only patients

undergoing abdominal aortic reconstruction, which limits generalisability. A large retrospective study that evaluated risk factors for AKI in non-cardiac surgical patients did not find intraoperative oliguria to be predictive of postoperative AKI.[24] However, this study examined only a single threshold of low UO (<0.5 mL kg^{-1} h^{-1}). This approach may miss the association between intraoperative UO and AKI even if patients with severe oliguria had a high incidence of AKI due to dilution by the larger patient population with UO immediately below the predetermined threshold with few AKI events. Furthermore, diuretics were used intraoperatively for some of the participants, which may have biased the results.

Our study was designed to overcome some of the limitations of these studies. First, it involved a large cohort of patients undergoing a broad spectrum of intra-abdominal procedures, which enabled a robust evaluation of relationships between exposure and outcome with sufficient statistical power. Second, we excluded patients receiving diuretics intraoperatively, which enabled us to analyse the relationship between intraoperative UO and AKI eliminating the effect of diuretics. Third, rather than evaluating predetermined values, we statistically identified the clinically relevant

threshold of UO. This approach allowed us to better relate the severity of intraoperative UO and AKI. To our knowledge, this is the first study to attempt to identify an optimal threshold of intraoperative UO associated with a differential risk of AKI.

In view of the results of recent randomised trials that perioperative fluid overloading is associated with poor postoperative outcomes,[8–11] intraoperative fluid restriction has been incorporated into various 'Enhanced Recovery After Surgery' protocols.[26–28] However, intraoperative fluid restriction may cause hypoperfusion of vital organs due to hypovolemia. Therefore, monitoring of organ hypoperfusion during the surgery is of increasing importance. Because UO is usually routinely monitored in patients undergoing major abdominal surgery, our result suggests that intraoperative UO of <0.3 mL kg^{-1} h^{-1} may serve as an early and easily available indicator of renal hypoperfusion or impending AKI. Urine flow rate of <0.3 mL kg^{-1} h^{-1} is similar to the classical definition of oliguria, i.e., UO of <400 mL day^{-1}, which is determined based on the minimum UO required to eliminate 300 mOsm day^{-1} in a maximum urine concentration of 1,200 mOsm kg^{-1}.[29]

Patients with intraoperative UO of <0.3 mL kg^{-1} h^{-1} were more likely to undergo

laparoscopic surgery. This finding is in line with previous studies that reported reduced diuresis during laparoscopic surgeries.[30 31] Possible mechanisms include a direct pressure effect of pneumoperitoneum on the renal vasculature resulting in reduced renal blood flow and the intraoperative release of stress hormones.[31] Therefore, there is a possibility that the threshold of clinically significant oliguria may be different between laparoscopic and non-laparoscopic patients. However, in our subgroup analysis, intraoperative UO of <0.3 mL kg^{-1} h^{-1} was significantly associated with AKI in both laparoscopic and non-laparoscopic patients.

We could not find a statistically significant association between intraoperative UO of 0.3–<0.5 mL kg^{-1} h^{-1} and AKI. Point estimate of odds ratio for intraoperative UO of 0.3–<0.5 mL kg^{-1} h^{-1} was 1.37, which is substantially smaller than that for intraoperative UO of <0.3 mL kg^{-1} h^{-1}. This finding suggests that the impact of intraoperative UO of 0.3–<0.5 mL kg^{-1} h^{-1} on AKI, if it exists, is small compared to that of intraoperative UO of <0.3 mL kg^{-1} h^{-1}. The widely used definition of intraoperative oliguria (<0.5 mL kg^{-1} h^{-1}) should be reconsidered because fluid replacement using a higher target of UO tends to increase the amount of fluid administered and may cause

harm.[8–11]

Strengths and limitations

Our study has several strengths. We found that our results remained robust after stratifying our analysis by various patient and operative variables. This suggests that the relationship between intraoperative UO and AKI does not change significantly depending on patient characteristics or types of surgery. We also confirmed the robustness of our findings through extensive sensitivity analyses. We had complete data on independent variables and the primary outcome in 99.9% of participants.

Our study has many limitations that should be considered when interpreting the results. Information on clinical risk factors of AKI were not prospectively collected; instead, they were retrieved from the electronic database and the electronic medical record system. Thus, effects of certain risk factors may have been biased. Findings of this observational study are merely an association and cannot imply causation; thus, we are unable to ascertain whether intraoperative management targeting urine flow rate at 0.3 mL kg^{-1} h^{-1} or more will reduce the risk of AKI. Future randomised trials are needed to

address this hypothesis. We could not clearly determine the duration of oliguria because our database contained only total UO and not hourly UO during the surgery. However, most patients with oliguria were assumed to have continuous reduction of UO for 3–4 h, considering that the duration of surgery was ≥3 h in 93.0% patients and ≥4 h in 79.5% patients. The single-centre design may limit the generalisability, and external validation is warranted to corroborate our findings. However, The incidence of AKI observed in our study was similar to recent large-scale studies reporting the incidence of AKI according to KDIGO criteria after intra-abdominal surgeries[19] or non-cardiac surgeries.[20 21] Our study included patients undergoing major abdominal surgery, so it is unclear whether our findings can be extrapolated to patients undergoing other surgeries. For example, Hori et al.[32] reported an independent association between urine flow rate of <1.5 mL kg^{-1} h^{-1} during cardiac surgery and AKI. Further studies are required to determine optimal thresholds of UO in various clinical settings.

In conclusion, among patients undergoing major abdominal surgery, intraoperative oliguria under 0.3 mL kg^{-1} h^{-1} was independently associated with postoperative AKI. Further research is required to determine whether intraoperative management targeting

urine flow rate at 0.3 mL kg^{-1} h^{-1} or more will reduce the risk of AKI.

Authors' Contributions

Conception of the study: T.M.

Study design: T.M. and S.M.

Data collection: T.M., M.H., S.M. and S.S.

Data analysis: T.M., Y.Y., M.H., S.M., S.S. and S.K.

Drafting the manuscript: T.M.

Editing and approval of the manuscript: T.M., Y.Y., M.H., S.M., S.S. and S.K.

Acknowledgements

We are grateful to Mr. Daisuke Sutou, Ms. Tomoko Hosoya and Mr. Yasushi Matsumoto (Medical Information Systems Section, Management Division, Kyoto University Hospital, Kyoto, Japan) for their assistance in data collection for this study.

Declaration of interest

None declared.

Funding

This work was supported in part by JSPS KAKENHI (grant number: 16K20092; T.M., principle investigator).

References

1. Butterworth JF, Mackey DC, Wasnick JD, eds. Morgan & Mikhail's Clinical Anesthesiology. 5th ed. New York: McGraw-Hill, 2013

2. Marino PL. The ICU Book. 4th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2014

3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; **45**: 486-552

4. McIntyre LA, Hébert PC, Fergusson D, Cook DJ, Aziz A; Canadian Critical Care Trials Group. A survey of Canadian intensivists' resuscitation practices in early septic shock. *Crit Care* 2007; **11**: R74

5. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. *Crit Care* 2011; **15**: R197

6. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*

2013;**41**: 580-637

7. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41

8. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812-8

9. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641-8

10. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103**: 25-32

11. McArdle GT, McAuley DF, McKinley A, Blair P, Hoper M, Harkin DW. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. *Ann Surg* 2009; **250**: 28-34

12. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum

creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982-92

13. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1-138

14. Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009; **110**: 505-15

15. Tokunaga K, Matsuzawa Y, Kotani K, et al. Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes* 1991; **15**: 1-5

16. Lemmens HJ, Brodsky JB, Bernstein DP. Estimating ideal body weight--a new formula. *Obes Surg* 2005; **15**: 1082-3

17. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49**: 1373-9

18. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple

confounders. *Am J Epidemiol* 2003; **158**: 280-7

19. Long TE, Helgason D, Helgadottir S, et al. Acute Kidney Injury After Abdominal Surgery: Incidence, Risk Factors, and Outcome. *Anesth Analg* 2016; **122**: 1912-20

20. Biteker M, Dayan A, Tekkeşin Aİ, et al. Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery. *Am J Surg* 2014; **207**: 53-9

21. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology* 2015; **123**: 515-23

22. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. *BMJ* 2009; **338**: b604

23. Alpert RA, Roizen MF, Hamilton WK, et al. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. *Surgery* 1984; **95**: 707-11

24. Kheterpal S, Tremper KK, Englesbe MJ, et al. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *Anesthesiology* 2007; **107**: 892-902

25. Goren O, Matot I. Perioperative acute kidney injury. *Br J Anaesth* 2015; **115**: ii3-14

26. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; **362**: 1921-8

27. Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800-9

28. Zargar-Shoshtari K, Connolly AB, Israel LH, Hill AG. Fast-track surgery may reduce complications following major colonic surgery. *Dis Colon Rectum* 2008; **51**: 1633-40

29. Klahr S, Miller SB. Acute oliguria. *N Engl J Med* 1998; **338**: 671-5

30. Nguyen NT, Perez RV, Fleming N, Rivers R, Wolfe BM. Effect of prolonged pneumoperitoneum on intraoperative urine output during laparoscopic gastric bypass. *J Am Coll Surg* 2002; **195**: 476-83

31. Nguyen NT, Wolfe BM. The physiologic effects of pneumoperitoneum in the morbidly obese. *Ann Surg* 2005; **241**: 219-26

32. Hori D, Katz NM, Fine DM, et al. Defining oliguria during cardiopulmonary bypass and its relationship with cardiac surgery-associated acute kidney injury. *Br J Anaesth* 2016; **117**: 733-40

Table 1. Patient characteristics and operative variables of 3,560 eligible patients.

	All patients (n = 3,560)	No AKI (n = 3,334)	AKI (n = 226)	P value
Age (years)	66 (56–73)	66 (56–73)	66 (60–73)	0.062
Male gender	2182 (61.3%)	2001 (60.0%)	181 (80.1%)	<0.001
Hypertension	1078 (30.3%)	961 (28.8%)	117 (51.8%)	<0.001
Diabetes mellitus	566 (15.9%)	508 (15.2%)	58 (25.7%)	<0.001
Active congestive heart failure	57 (1.6%)	50 (1.5%)	7 (3.1%)	0.09
Ascites	294 (8.3%)	269 (8.1%)	25 (11.1%)	0.132
ASA-PS (1/2/3/4/missing)	991/2297/231/3/38	975/2116/206/2/35	16/181/25/1/3	<0.001
Preoperative SCr (μmol L^{-1})	62.8 (53.0–78.7)	61.9 (53.0–77.8)	70.7 (61.9–84.9)	<0.001
Preoperative estimated glomerular filtration rate (mL min^{-1} 1.73 m^{-2})	75.4 (64.1–87.9)	75.4 (64.5–88.0)	72.9 (58.8–86.0)	0.004
AKI risk index				<0.001
Class 1	1278 (35.9%)	1248 (37.4%)	30 (13.3%)	
Class 2	1174 (33.0%)	1106 (33.2%)	68 (30.1%)	
Class 3	750 (21.1%)	672 (20.2%)	78 (34.5%)	
Class 4	283 (7.9%)	244 (7.3%)	39 (17.3%)	
Class 5	75 (2.1%)	64 (1.9%)	11 (4.9%)	
Type of surgery				<0.001
Liver	1135 (31.9%)	1034 (31.0%)	101 (44.7%)	

Colorectal	1054 (29.6%)	1012 (30.4%)	42 (18.6%)	
Gastric	627 (17.6%)	593 (17.8%)	34 (15.0%)	
Pancreatic	525 (14.7%)	486 (14.6%)	39 (17.3%)	
Oesophageal	189 (5.3%)	183 (5.5%)	6 (2.7%)	
Complex	30 (0.8%)	26 (0.8%)	4 (1.8%)	
Laparoscopic surgery	1860 (52.2%)	1800 (54.0%)	60 (26.5%)	<0.001
Emergency surgery	46 (1.3%)	41 (1.2%)	5 (2.2%)	0.212
Epidural anaesthesia	1721 (48.3%)	1589 (47.7%)	132 (58.4%)	0.002
Duration of surgery (min)	352 (257–468)	345 (254–461)	439 (329–591)	<0.001
Intraoperative fluid administration				
Crystalloid (mL kg^{-1})	51.2 (36.8–71.8)	50.5 (36.5–71.2)	59.5 (44.2–81.9)	<0.001
Colloid (mL kg^{-1})	0.0 (0.0–8.5)	0.0 (0.0–8.3)	7.8 (0.0–14.2)	<0.001
Intraoperative blood loss				<0.001
<10 mL kg^{-1}	2770 (77.8%)	2669 (80.1%)	101 (44.7%)	
10–<20 mL kg^{-1}	453 (12.7%)	403 (12.1%)	50 (22.1%)	
≥20 mL kg^{-1}	337 (9.5%)	262 (7.9%)	75 (33.2%)	
Intraoperative red blood cell transfusion	298 (8.4%)	231 (6.9%)	67 (29.6%)	<0.001
Intraoperative UO (mL kg^{-1} h^{-1})	0.81 (0.47–1.40)	0.82 (0.47–1.41)	0.69 (0.41–1.26)	0.009
Net fluid balance during surgery (mL kg^{-1})	43.2 (31.4–59.9)	42.8 (31.1–59.4)	50.8 (36.0–68.8)	<0.001
Intraoperative vasopressor infusion	324 (9.1%)	273 (8.2%)	51 (22.6%)	<0.001

Data are presented as median (interquartile range) or numbers (percentages). ASA-PS, the American Society of Anaesthesiologists physical status; SCr, serum creatinine; AKI, acute kidney injury; UO, urine output.

Table 2. Models to predict postoperative AKI.

	Patient/operative variables only		Patient/operative variables and Intraoperative UO	
	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value
AKI Risk Index				
Class 1	1 (Reference)		1 (Reference)	
Class 2	2.31 (1.48–3.62)	<0.001	2.26 (1.44–3.54)	<0.001
Class 3	3.82 (2.44–5.97)	<0.001	3.69 (2.36–5.78)	<0.001
Class 4	5.91 (3.53–9.89)	<0.001	5.43 (3.23–9.12)	<0.001
Class 5	7.39 (3.42–15.90)	<0.001	7.35 (3.38–16.00)	<0.001
Type of surgery				
Liver	1 (Reference)		1 (Reference)	
Colorectal	0.73 (0.47–1.13)	0.155	0.66 (0.42–1.02)	0.062
Gastric	1.06 (0.66–1.69)	0.805	0.87 (0.54–1.41)	0.576
Pancreatic	0.55 (0.37–0.83)	0.004	0.57 (0.38–0.86)	0.008
Oesophageal	0.55 (0.23–1.31)	0.177	0.58 (0.24–1.39)	0.224
Complex	1.17 (0.38–3.66)	0.785	1.20 (0.39–3.74)	0.754
Intraoperative blood loss				
<10 mL kg^{-1}	1 (Reference)		1 (Reference)	
10–<20 mL kg^{-1}	3.03 (2.00–4.59)	<0.001	3.22 (2.12–4.91)	<0.001
≥20 mL kg^{-1}	5.58 (3.71–8.40)	<0.001	6.03 (3.97–9.14)	<0.001
Intraoperative vasopressor infusion	1.64 (1.12–2.39)	0.010	1.67 (1.15–2.44)	0.008
Intraoperative UO				
≥0.3 mL kg^{-1} h^{-1}			1 (Reference)	
<0.3 mL kg^{-1} h^{-1}			2.65 (1.77–3.97)	<0.001

AKI, acute kidney injury; UO, urine output; aOR, adjusted odds ratio; CI, confidence interval.

Table 3. Reclassification table comparing models with and without intraoperative urine output as a predictor of AKI.

	No. of patients			Net reclassification
	Total	Reclassified up	Reclassified down	improvement (95% CI)
AKI present	226	50	176	-0.558 (-0.623 to -0.490)
AKI absent	3334	472	2862	0.717 (0.701 to 0.732)
Total	3560	522	3038	0.159 (0.049 to 0.270)

AKI, acute kidney injury; CI, confidence interval.

Figure legends

Fig. 1 Flow diagram of the study population. We first identified adult patients undergoing a major abdominal surgery under general anaesthesia from those undergoing surgery in the Departments of Gastrointestinal Surgery, Hepatobiliary Pancreatic Surgery and Transplantation and Pediatric Surgery of Kyoto University Hospital using patient age, procedure name and anaesthetic technique as recorded in the electronic database. Then, we performed medical record review for further assessment for eligibility.

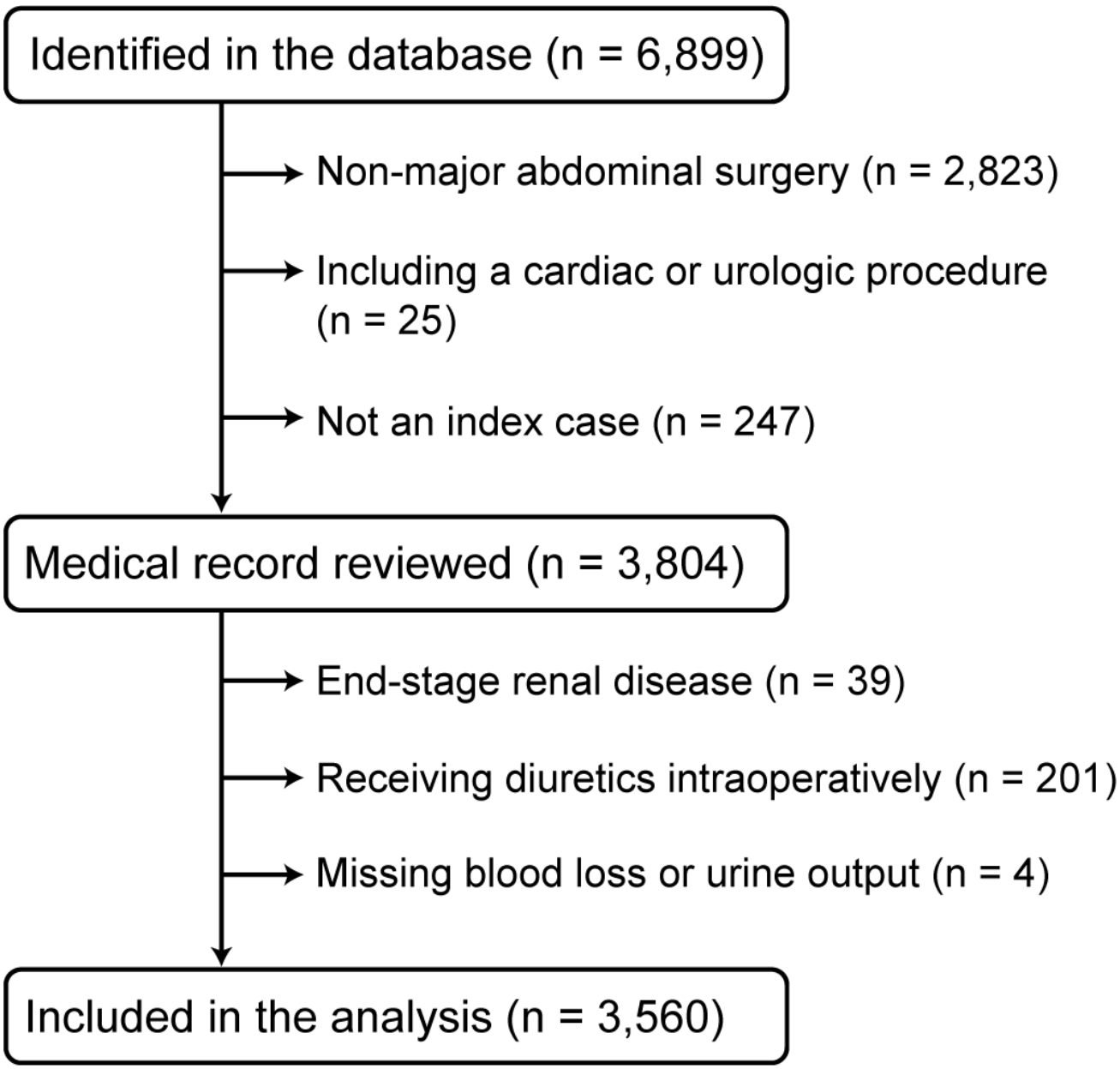


Fig. 2 Cubic spline function curves of the unadjusted relationship between intraoperative urine output and the probability of AKI. Shades represent 95% confidence intervals. Panel A includes a range of intraoperative urine output from 0 to 4 mL kg^{-1} h^{-1}, and panel B includes that from 0 to 1 mL kg^{-1} h^{-1}.

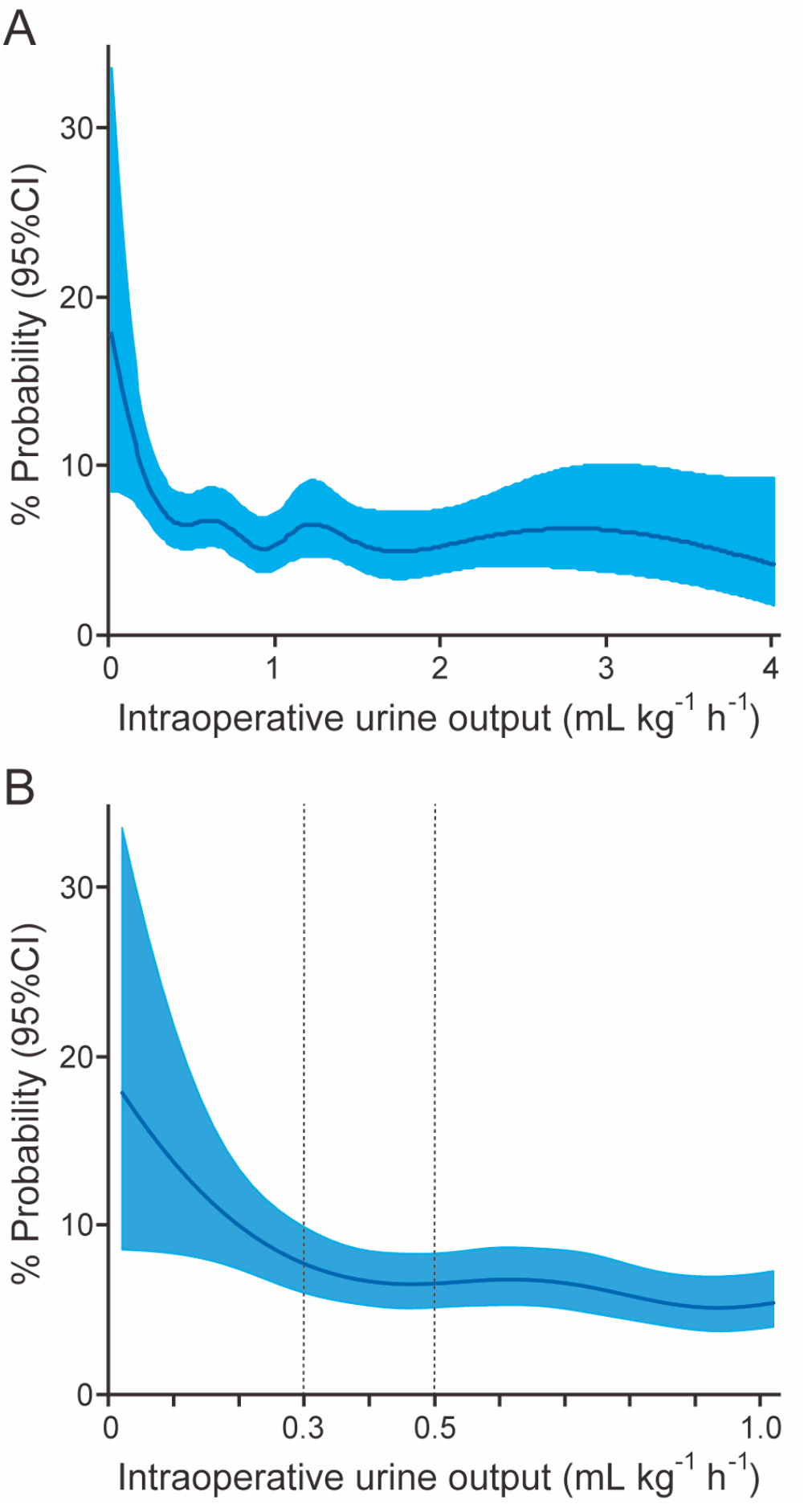
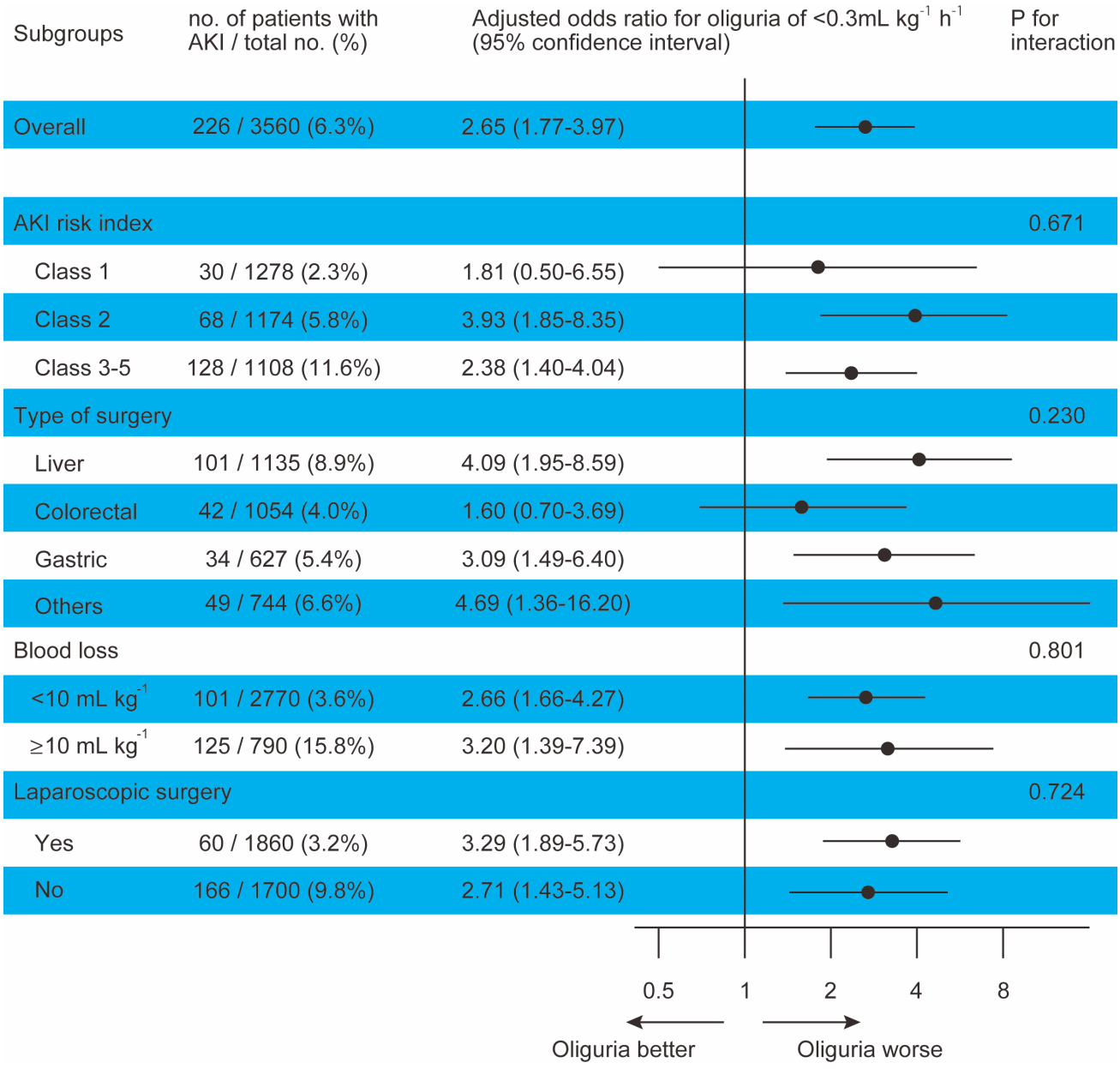


Fig. 3 Subgroup analyses stratified by patient and operative variables.



Supplementary Content

Table S1. Definitions of variables collected by questionnaire.

Variables	Definitions
Age	In years
Gender	Male or female
Weight and height	Most recent value measured before the surgery
Hypertension	History of hypertension requiring anti-hypertensive medication recorded in the medical chart
Diabetes mellitus	A diagnosis of diabetes requiring oral medication or insulin
Active congestive heart failure	Documented in the patient's chart within 30 days before surgery A diagnosis of congestive heart failure requiring diuretics
Ascites	Documented in the patient's chart within 30 days before surgery
ASA-PS	1 to 5, recorded in the electronic database
Preoperative SCr	Most recent value measured before surgery
Preoperative estimated glomerular filtration rate	In mL min^{-1} 1.73 m^{-2}, calculated from preoperative SCr using a formula validated in Japan (Am J Kidney Dis 2009; 53: 982-92)
AKI risk index	Class 1 to 5, assigned based on age, gender, emergency surgery, intra-peritoneal surgery, diabetes mellitus, active congestive heart failure, ascites, hypertension and preoperative renal insufficiency (Anesthesiology 2009; 110: 505–15).
Type of surgery	Grouped into six categories by operation site (colorectal, gastric, liver, pancreatic, oesophageal and complex) according to procedure name recorded in the electronic database
Laparoscopic surgery	Identified using procedure name recorded in the electronic database
Emergency surgery	An emergency procedure performed within 12 h after admission or after the onset of related symptoms

Epidural anaesthesia	Defined as an epidural catheter placement documented in the anaesthesia chart, regardless of duration of catheter placement
Duration of surgery	In minutes, from skin incision to skin closure
Duration of operating room stay	In minutes, from entering to leaving the operating room
Intraoperative crystalloid administration	In mL kg^{-1}, extracted from the electronic database
Intraoperative colloid administration	In mL kg^{-1}, extracted from the electronic database
Intraoperative blood loss	In mL kg^{-1}, extracted from the electronic database
Intraoperative red blood cell transfusion	Administration of red blood cells during surgery
Intraoperative UO	In mL kg^{-1} h^{-1}, extracted from the electronic database
Net fluid balance during the surgery	In mL kg^{-1}, calculated by subtracting blood loss and UO from volume of fluid and blood products administered
Intraoperative vasopressor infusion	Use of continuous infusion of vasopressor (phenylephrine, dopamine, noradrenaline, adrenaline or vasopressin) during the operating room stay, documented in the anaesthesia chart
AKI	Defined as stage ≥1 AKI according to the Kidney Disease: Improving Global Outcomes guidelines AKI stages were assigned based on SCr change within 7 days of surgery. The most recent SCr measured before surgery was used as the baseline value.
Postoperative length of stay	Number of days from the surgery to discharge from the hospital
In-hospital mortality	Death during the hospital stay for the surgery

ASA-PS, the American Society of Anaesthesiologists physical status; SCr, serum creatinine; AKI, acute kidney injury; UO, urine output.

Table S2. Cut-off point analysis for intraoperative UO and postoperative AKI.

Intraoperative UO (cut-off points, mL kg^{-1} h^{-1})	aOR (95% CI)	P-value
0.1	2.13 (0.69–6.64)	0.190
0.2	3.00 (1.74–5.19)	0.00008
0.3	2.65 (1.77–3.97)	<0.00001
0.4	2.09 (1.44–3.04)	0.00011
0.5	1.92 (1.36–2.70)	0.00018
0.6	2.01 (1.46–2.76)	0.00002
0.7	1.97 (1.45–2.69)	0.00002
0.8	2.02 (1.47–2.76)	0.00001
0.9	1.89 (1.38–2.59)	0.00008
1.0	1.61 (1.17–2.21)	0.00352

Every possible threshold of intraoperative UO at intervals of 0.1 mL kg^{-1} h^{-1} was evaluated using a multivariable model with the AKI risk index and operative variables.

UO, urine output; AKI, acute kidney injury; aOR, adjusted odds ratio.

Table S3. Patient characteristics and operative variables stratified by intraoperative UO.

	UO ≥0.3 mL kg^{-1} h^{-1} (n = 3157)	UO <0.3 mL kg^{-1} h^{-1} (n = 403)	P-value
Age (years)	66 (56–73)	67 (59–75)	0.008
Male gender	1902 (60.2%)	280 (69.5%)	<0.001
Hypertension	925 (29.3%)	153 (38.0%)	0.001
Diabetes mellitus	509 (16.1%)	57 (14.1%)	0.347
Active congestive heart failure	47 (1.5%)	10 (2.5%)	0.139
Ascites	257 (8.1%)	37 (9.2%)	0.501
ASA-PS (1/2/3/4/missing)	888/2026/207/2/34	103/271/24/1/4	0.289
Preoperative SCr (μmol L^{-1})	61.9 (53.0–76.9)	70.7 (56.6–82.2)	<0.001
Preoperative estimated glomerular filtration rate (mL min^{-1} 1.73 m^{-2})	75.8 (64.9–88.5)	71.3 (60.3–82.1)	<0.001
AKI risk index			
Class 1	1165 (36.9%)	113 (28.0%)	0.002
Class 2	1032 (32.7%)	142 (35.2%)	
Class 3	659 (20.9%)	91 (22.6%)	
Class 4	236 (7.5%)	47 (11.7%)	
Class 5	65 (2.1%)	10 (2.5%)	
Type of surgery			
Liver	1077 (34.1%)	58 (14.4%)	<0.001
Colorectal	874 (27.7%)	180 (44.7%)	
Gastric	484 (15.3%)	143 (35.5%)	
Pancreatic	513 (16.2%)	12 (3.0%)	
Oesophageal	181 (5.7%)	8 (2.0%)	
Complex	28 (0.9%)	2 (0.5%)	
Laparoscopic surgery	1531 (48.5%)	329 (81.6%)	<0.001
Emergency surgery	45 (1.4%)	1 (0.2%)	0.056
Epidural anaesthesia	1653 (52.4%)	68 (16.9%)	<0.001
Duration of surgery (min)	365 (265–480)	279 (224–348)	<0.001
Intraoperative fluid administration			
Crystalloid (mL kg^{-1})	54.4 (39.3–74.4)	34.7 (26.6–44.5)	<0.001
Colloid (mL kg^{-1})	0.0 (0.0–9.0)	0.0 (0.0–0.0)	<0.001

Intraoperative blood loss			<0.001
<10 mL kg^{-1}	2397 (75.9%)	373 (92.6%)	<0.001
10–<20 mL kg^{-1}	435 (13.8%)	18 (4.5%)	
≥20 mL kg^{-1}	325 (10.3%)	12 (3.0%)	
Intraoperative red blood cell transfusion	285 (9.0%)	13 (3.2%)	<0.001
Intraoperative UO (mL kg^{-1} h^{-1})	0.90 (0.57–1.51)	0.23 (0.17–0.26)	<0.001
Net fluid balance during the surgery (mL kg^{-1})	45.3 (32.6–61.8)	33.3 (25.3–42.2)	<0.001
Intraoperative vasopressor infusion	303 (9.6%)	21 (5.2%)	0.003

Data are presented as median (interquartile range) or numbers (percentages).

ASA-PS, the American Society of Anaesthesiologists Physical Status; SCr, serum creatinine; AKI, acute kidney injury; UO, urine output.

Table S4. Sensitivity analyses. Multivariable adjustment for AKI risk index and operative variables was performed in all analyses.

Model	No. of patients with AKI/total no. (%)	Adjusted odds ratio of intraoperative oliguria (95% CI)	P-value
Entire sample	226/3,560 (6.3%)	2.65 (1.77–3.97)	<0.001
AKI redefined on the basis of SCr concentrations only up to 2 days postoperatively	197/3,560 (5.5%)	3.06 (1.98–4.71)	<0.001
Using stage 2–3 AKI as the outcome	39/3,560 (1.1%)	2.86 (1.13–7.22)	0.026
adjusting for the duration of surgery	226/3,560 (6.3%)	2.74 (1.82–4.11)	<0.001
Using ideal body weight to calculate urine output per body weight*	226/3,553 (6.4%)	2.24 (1.46–3.43)	<0.001
Excluding patients who received intraoperative vasopressor infusion	175/3,236 (5.4%)	2.74 (1.77–4.23)	<0.001
Excluding patients who received diuretics preoperatively	206/3407 (6.0%)	2.83 (1.84–4.34)	<0.001
Excluding emergency surgeries	221/3,514 (6.3%)	2.72 (1.81–4.09)	<0.001

*Seven patients whose data on height was missing were excluded from the analysis. AKI, acute kidney injury; SCr, serum creatinine.

Fig. S1 Cubic spline analysis of the association between intraoperative blood loss and postoperative AKI. The test for non-linearity was statistically significant (P <0.001). The probability of AKI increased as a function of intraoperative blood loss until a blood loss of about 20 mL kg^{-1}, after which it continued to increase with increased blood loss but at a lower rate. AKI, acute kidney injury.